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EXAMINER
CANELLA, KAREN A

ART UNIT	PAPER NUMBER
1642	

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15

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Applicati n No.	Applicant(s)	
	09/872,364	THASTRUP ET AL.	
	Examin r	Art Unit	
	Karen A Canella	1642	

-- The MAILING DATE of this communicati n appears on the cover sheet with the correspondence address --

Period f r Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-12,14,18,20,21,23,26,28-32 and 35-47* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-12,14,18,20,21,23,26,28-32 and 35-47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *13* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 19, 27, 33 and 34 have been canceled. Claims 35-47 have been added. Claims 1-12, 14, 18, 20, 21, 23, 26, 28-32 and 35-47 are pending and examined on the merits.

Claim 35 is objected to because of the following informalities: Claim 35 , line 5 recites "chromophore is substituted with and amino acid". Appropriate correction is required.

Claims 28-32 are objected to under 37 CFR 1.75 as being a substantial duplicate of claims 3-7, respectively. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claims 1-12, 14, 18, 20, 21, 23, 26, 28-33 and 35-47 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The instant claims recite the limitations of Green Fluorescent Protein. The metes and bound of what constitutes a "green fluorescent" protein cannot be determined as it is unclear whether the recitation of "green fluorescent protein is intended to limit the protein to that isolated from A victoria, or if other green fluorescent proteins, such as those isolated from other marine organisms such as the coral, as included within this definition. Also it is unclear if "green" is intended to limit the emission spectrum to a specific range of wavelengths, or if variants of the green florescent protein as isolated from A vicotria, which exhibit a differing emission spectrum, such as the red-shifted variant, are included within the definition of a green fluorescent protein.

Further, it is unclear if the terms encompass proteins having a green fluorescence emission spectrum, wherein said proteins are not obtained from a fluorescent jellyfish, such as proteins which are produced by site-directed mutagenesis in a laboratory. The specification state on page 7, lines 11-24 that a preferred embodiment of the invention is the green fluorescent protein derived from A victoria,. However, this does not constitute a limiting definition for green fluorescent protein. Further, the specification states on page 7, lines 23-24 that novel fluorescent proteins may be derived from R reniformis. Thus, the specification is contemplating fluorescent proteins which are not limited to those found in A victoria. Accordingly, for purpose of examination, all alternatives of fluorescent protein will be considered without regard to origin or color of emission spectra.

Claims 14 and 23 are vague and indefinite in the recitation of "green fluorescent protein" according to claims 1 and 18, respectively. It is unclear if only the substituted GFP or both substituted and unsubstituted are encompassed by the recitation of GFP. For purpose of examination, both alternatives will be considered.

Claims 18, 23, 35, 36-47 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

(A) As drawn to new matter

New claim 37 embodies the nucleic acid of claim 35 wherein said GFP is wild-type GFP. The specification as filed does not define a "wildtype" green fluorescent protein or contemplate a "wild-type" green fluorescent protein.

(B) As drawn to nucleic acids encoding a genus of proteins

The instant claims are drawn to the nucleic acids encoding fluorescent proteins which minimally comprise a fluorescent chromophore of SerTyrGly, SerHisGly, ThrHisGly or ThrTyrGly , immediately followed by Leu, Ile, Val, Gly, or Ala . It is noted that claim 18, lines 4-5 characterizes the fluorescent protein as "substituted with at least an amino acid". Thus, claim 18 clearly contemplates more than one alterations to the structure of the green fluorescent protein. The specification sets forth SEQ ID NO:16, 18, 20 and 22 as fluorescent proteins of the instant invention. For the reasons set forth in the rejection under 112, second above, the metes and bounds of the instant claims cannot be determined as the structure and function of the proteins encoded thereby are not limited. The specification teaches variants of SEQ ID NO:22, wherein amino acid residue 64 is either Leu, Ile, Val, Gly, or Ala and wherein residues 65-67 are SerTyrGly, SerHisGly, ThrHisGly or ThrTyrGly. The disclosed variants of SEQ ID NO:22 (SEQ ID NO:16, 18 and 20) fail to anticipate the claimed genus of proteins because the genus encompasses proteins having an unlimited number of structural alterations, in addition to those disclosed, in addition to having an emission spectrum which is not confined to a range of wavelengths which would be green. Thus, the genus of proteins is variant, encompassing numerous structural and functional modifications, as evidenced from the art rejections below. One of skill in the art would conclude that applicant did not disclose a representative number of species to describe the genus of proteins on which the genus of nucleic acids depends.

Claim Rejections - 35 USC § 102

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 18, 23, 35, 36, 37, 40, 43, 44, 45, 46, 47 are rejected under 35 U.S.C. 102(a) as being anticipated by Ward et al (WO 95/21191).

Claim 18 is drawn to a nucleotide sequence encoding a green fluorescent protein having am amino acid sequence in which the amino acid Phe immediately upstream of the chromophore is substituted with at least an amino acid selected from the group consisting of Leu, Ile, Val, Gly, and Ala, wherein said chromophore has an amino acid sequence selected from the group consisting of SerTyrGly, SerHisGly, ThrHisGly and ThrTyrGly, and wherein said substituted GFP exhibits increased fluorescence at the same wavelength at a temperature of 30 degrees or above, relative to a GFP lacking the above substitution, when expressed in a host cell. Claim 23 is drawn to a nucleic aid molecule comprising a nucleotide sequence encoding a protein of interest fused to a nucleotide sequence encoding a green fluorescent protein according to claim 18. Claim 35 is drawn to a nuclei c acid molecule comprising a nucleotide sequence encoding a fluorescent protein derived from a green fluorescent protein, said fluorescent protein having an amino acid sequence in which the amino acid Phe immediately upstream of the chromophore is substituted with an amino acid selected from the group consisting of Leu, Ile, Val, Gly, and Ala, and wherein said chromophore has an amino acid sequence selected from the group consisting of SerTyrGly, SerHisGly, ThrHisGly and ThrTyrGly , and wherein said protein exhibited increased fluorescent at the same wavelength at a temperature of 30 degrees or above, relative to the protein lacking the above substitution when expressed in a host cell. Claim 36 embodies the nucleic acid according to claim 35 herein said GFP is A victoria GFP or R reniformis GFP. Claim 37 embodies the nucleic acid of claim 1 wherein said GFP is wild-type GFP. Claim 42 embodies the nucleic acid of claim 18 wherein a Gly residue is substituted for the Phe residue.

Claim 43-45 embody the nucleic acid molecule of claim 18 wherein said substituted GFP exhibits increased fluorescence at the same wavelength and at a temperature of from 32 degrees to 39 degrees, from 35 degrees to 38 degrees and at a temperature of about 37 degrees, respectively. Claim 46 embodies the nucleic acid of claim 18 wherein the GFP is derived from A. victoria or R. reniformis. Claim 47 is drawn to a nucleic acid sequence comprising a nucleotide sequence encoding a protein of interest fused to a nucleotide sequence according to claim 35.

Ward et al disclose the nucleic acid sequence of SEQ ID NO:2) encoding a modified A victoria GFP (SEQ ID NO: 1), wherein said modified sequence comprise the chromophore ThrTyrGly (residues 38-40 of SEQ ID NO:1), which is followed immediately upstream by the residue Ala (residue 37). Ward et al disclose expression vectors comprising said sequence wherein said vector is fused to a protein of interest, wherein said protein of interest confers drug resistance, such as ampicillin (page 12, lines 7-11), or wherein said protein of interest is a luciferase (page 12, lines 18-27). Ward et al do not identify residues 37-40 as a chromophore, or compare the level of fluorescence to a protein having a Phe at residue 37, however, the properties of having the claimed chromophore preceded by a Gly residue are the same as that claimed, therefore, the limitation of increased fluorescence at the same wavelength and at the specified temperatures to a protein having a Phe residue at position 37 would be inherent in the protein disclosed by Ward et al.

Claims 18, 23, 35, 37, 42, 43, 44, 45, 47are rejected under 35 U.S.C. 102(b) as being anticipated by Zhang et al (Journal of Biological Chemistry, 1992, Vol. 267, pp. 23759-23766)

or Mehra et al (Journal of Biological chemistry, 1989, Vol. 264, pp. 19747-19753), The specific embodiments of the claims are set forth above.

Zhang et al disclose the proteins of Yop51 and a Yop51 truncation mutant, wherein said Yop51 and truncation mutants are proteins having the claimed chromophore at residues 307-309 (ThrTyrGlu) which is immediately preceeded by a Glu residue at position 306 (Figure 1B, page 23760). Zhang et al disclose expression vectors comprising nucleic acid encoding the Yop51 proteins and wherein said vectors also encode a drug resistance protein (page 23760, under the heading "Construction of the Expression Plasmids" and especially page 23760, second column, lines 9-11, "pT7-7") which fulfill the limitation of "a protein of interest". Zhang et al disclose that the Yop51 proteins are fluorescent proteins (page 23763, under the heading "Spectroscopic Characterization of the Yersinia PTPases", and figure 5).

Mehra et al disclose the protein of metallothionein II wherein said protein has the claimed chromophore at residues 45-47 (SerHisGly)) which is immediately preceeded by a Gly residue at position 44 (page 19749, Figure 8). Mehra et al disclose the cloning of said sequence and the expression in E coli (page 19749, under the heading "Cloning and Sequencing of the MT-I Gene", thus the expression of a drug resistance protein fulfills the specific limitation of a protein of interest. Mehra et al disclose that the MT-I protein is fluorescent (abstract, and page 19749, column 1, second paragraph)

Neither Zhang et al nor Mehra et al identify the claimed chromophores, or compare the level of fluorescence to a protein having a Phe immediately preceding said chromophore, however, the properties of having the claimed chromophore preceeded by a Gly residue are the same as that claimed, therefore, the limitation of increased fluorescence at the

same wavelength and at the specified temperatures to a protein having a Phe residue immediately preceding the claimed chromophore would be inherent in the proteins disclosed by Zhang et al and Mehra et al.

The rejection of claims 14 and 23 under 35 U.S.C. 102(e) as being anticipated by Chalfie et al (US 5,491,084) is maintained. The specific embodiments of the claims are recited above. It is noted that the metes and bound of claims 14 and 23 cannot be determined as it is unclear if the GFP of claims 14 and 23 constitutes the substituted or unsubstituted green fluorescent proteins of claims 1 and 18.

Chalfie et al discloses a DNA molecule comprising a suitable regulatory element operatively linked to the DNA encoding the GFP from A victoria (column 4, line 65 to column 5, line 10). Chalfie et al further disclose the linkage of the DNA encoding the GFP protein with the DNA encoding a protein of interest (column 4, lines 30-45 and lines 52-54 and column 5, lines 23-29). Chlafie et al disclose host cells comprising said expression vector (column 5, lines 12-20 and column 6, lines 59-61). The disclosure of Chlafie et al fulfills the specific limitations of claims 14 and 23 with respect to the unsubstituted GFPs of claims 1 and 18

The rejection of claim 14 under 35 U.S.C. 102(e) as being anticipated by Tsein et al (US 5,625,048) is maintained. Claim 23 is also rejected under 35 U.S.C. 102(e) as being anticipated by Tsein et al (US 5,625,048).

The specific embodiments of the claims are recited above. It is noted that the metes and bound of claims 14 and 23 cannot be determined as it is unclear if the GFP of claims 14 and 23 constitutes the substituted or unsubstituted green fluorescent proteins of claims 1 and

18. Tsein et al disclose a nucleic acid molecule comprising a DNA encoding a functional analog of GFP fused to a protein of interest (claims 15-17), and thus fulfills the specific limitations of claims 14 and 23 with respect to the unsubstituted GFPs of claims 1 and 18.

Claim Rejections - 35 USC § 103

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 18, 35, 42, 43, 44 and 45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Marche et al (Biochemistry, 1976, Vol. 15, pp. 1976), in view of what is well known in the art, as exemplified by Watson et al (The Molecular Biology of the Gene, 1987, Vol. I, page 437). The specific embodiments of the claims are recited above.

Marche et al disclose the $[Gly]^3$ analog of the luliberin peptide which comprises the claimed chromophore at residues 4-6 (SerThrGly), and which in the $[Gly]^3$ analog is immediately preceeded by Gly. Marche et al do not disclose the nucleic acid encoding said peptide.

It is well known in the art that nucleic acids encode proteins by means of a triplet genetic code, as exemplified by Table 15-4 in Watson et al.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to deduce the sequence of the nucleic acid encoding the luliberin peptide. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of the Wastson et al regarding the genetic code.

The provisional rejection of claims 1-3, 8, 9, 10, 11, 12, 18-21, 26, 28, 29 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 10-15 and newly added claims 28-31 and 33 of copending Application No. 09/619,310 is maintained for reasons of record. Claims 30-32 and 35-46 are also rejected for the same reasons of record. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims in the '310 application anticipate the instant claims drawn to SEQ ID NO:16, 18 and 20 as well as instant claims 18 and 35 drawn to a nucleic acid molecule comprising a nucleotide sequence encoding a green fluorescent protein having the which has been modified by an amino acid substitution of Leu, Ile, Val, Gly or Ala immediately upstream of the chromophore.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

All other rejections and objections as set forth in Paper No. 12 are withdrawn.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Canella whose telephone number is (703) 308-8362. The examiner can normally be reached on Monday through Friday from 8:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Karen A. Canella

Karen A. Canellá, Ph.D.

Patent Examiner, Group 1642

8/25/03